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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,656	06/20/2003	Bill E. Cham	13131-0310 (44378-282108)	8075

23370 7590 04/17/2006

JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
ATLANTA, GA 30309

EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,656	CHAM ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,28-31 and 33-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,28-31 and 33-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/311,679.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 2, 2006 has been entered. Claims 1, 2, 28-31 and 33-51 are pending and under examination.

2. The following objection and rejections are withdrawn in view of Applicant's amendment:

- The objection to claim 34 for improper grammar is withdrawn in view of Applicant's amendment.
- Claims 39 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of lack of antecedent basis, is withdrawn in view of Applicant's amendment.
- The rejection of claims 2, 28-31, 37, 39 and 40 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the claims encompasses protection against HIV infection, is withdrawn in view of Applicant's amendment.

Priority

3. The Office notes that the instant claims have priority to provisional application, USSN 60/390,066, filed June 20, 2002. The instant claims are drawn to subject matter that was not present in the parent application, USSN 10/311,679. The subject matter that is entitled only to the benefit of the filing date of the provisional application is, "at least one exposed epitope not usually presented to an immune system of the animal or the human by the non-delipidated viral particle", among other newly presented subject matter. Therefore, the art rejections are based on the date of priority for this application, June 20, 2002.

Claim Rejections - 35 USC § 102

4. (*New Rejection*) The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 28-31 and 33-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Barrett *et al.* (US 6,136,321, "Barrett", filed February 10, 1998). The claims are drawn to a modified immunodeficiency virus particle comprising at least a partially delipidated immunodeficiency virus particle that initiates a positive immune response in an animal or human patient and incites protection against an infectious organism. (The infectious organism is understood to be the same species (HIV, SIV, FIV, etc.) as the delipidated viral particle.) The specification indicates that the viral particle is modified by exposing a non-delipidated viral particle to a delipidation process wherein the lipid content of a virus is reduced. The particle is

not infectious, yet remains immunogenic and exposes epitopes that are not usually presented to the immune system by untreated virus. The virus particle proteins are structurally changed by the delipidation process on, in or near the surface of the virus (page 20, lines 10-23). Particular epitopes include gag, p6, gp66, gp41, p27 or env. The modified viral particle retains over 90% of major protein constituents.

Barrett discloses a method of inactivating lipid-enveloped viruses. The method involves a non-ionic detergent from the group of polysorbates for a period of time to completely inactivate the virus particle without affecting its structural integrity and particularly the biological activity of its surface and envelope proteins (col. 3, lines 1-15). Viruses that are inactivated by the disclosed method include all enveloped viruses, including retroviruses, such as SIV, HIV-1 and HIV-2 (col. 2, lines 50-59, and col. 3, lines 38-45). Barrett discloses that the biological activity of HIV's CD4 binding function is not affected by the inactivation (col. 3, lines 50-52).

In Examples 1-3, Barrett describes the inactivation of HIV-1, HIV-2, influenza and pseudorabies virus (PRV). The viruses are purified via sucrose gradient centrifugation and dialysis. The purified preparation is admixed with octyl glucoside or polysorbate 80 for one hour. The presence of HIV proteins was measured after the inactivation, and gp120 and gp140 were detected.

Barrett uses polysorbate 80 in particular because it is considered to be compatible for humans and is frequently used in foods and cosmetics (col. 5, lines 12-18). The concentration of the polysorbate is in a range of between 1% and 25%. Barrett also discloses that the inactivated virus may be formulated with pharmaceutically acceptable and physiologically acceptable

carriers, such as ionized water, PBS, salts, amino acids and non-ionic detergents for stabilizing purposes (col. 6, lines 14-27). The composition may also contain an adjuvant (immunostimulant) such as mineral oils, immunomodulators and immunopotentiators (col. 6, lines 28-37).

The claimed method steps of making the compositions do not lend patentability to the claims. The method steps are not expected to result in a structurally different and functionally different product than Barrett because the method steps of Barrett use the same organic solvent as Applicant: polysorbates (surfactants). Even in the claims that recite alcohols as the organic solvent, one expects the resulting viral particle to be the same as Barrett's viral particle that has reduced lipid content yet remains biologically active. Therefore, the invention as a whole is anticipated by the prior art.

SC 4/13/06

48

5. Claims 1, 29-31, 33-47, and 49-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Naficy (US Patent 5,419,759). Naficy discloses a method of treating HIV comprising an apheresis method that treats HIV infected components of a patient's blood with diethyl ether to kill infected cells and destroy the lipid envelope of the virus. The patient's blood containing delipidated virus (substantially free of the ether) is then returned to the patient (abstract and col. 9, lines 12-47). Since the particles of Naficy are made by the exposure to an ether, as are Applicant's modified particles, the viral particles of Naficy are delipidated and therefore anticipate the instant claims.

With regard to the new limitation presented in claim 48 about the concentration of the solvent, Applicant has not demonstrated that 5% ether results in destruction of the HIV envelope.

Applicant has demonstrated destruction of HIV envelope with 5% butanol, not ether. Any conclusions about Naficy's method based on Applicant's experiment cannot be relied upon because they are unconvincing opinion evidence.

With regard to the new limitation presented in claim 51 about the reduction of infectivity being no more than 2.5 log units (as compared to a non-modified virus), the claimed components of the product are the same as those in Naficy. Any properties of the components of the product are expected to be present in Naficy's product because they are comprised of the same components.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that Naficy's particles do not expose previously unexposed epitopes. Naficy does not teach or suggest any immunogenic properties of the partially delipidated viral particles, particularly the initiation of a positive immune response.
  - In response to this argument, the Office considers the particles of Naficy and Applicant to be the same. Both are treated with ether, thus delipidated to some degree. One of ordinary skill would expect that the particles exhibit the same properties given their similar methods of production. Absent evidence to the contrary, the particles' functions are expected to be the same.
- Applicant argues that Naficy's method destroys the lipid envelope of HIV, rendering the virus unable to penetrate and infect healthy cells. Applicant asserts that Naficy's method begins by delipidating plasma containing cell-free virus and cell infected with

virus, followed by returning plasma containing the killed cells to the patient. Applicant asserts that returning the killed cells could be toxic to the patient. Applicant argues that Applicant's method separates both red and blood cells from plasma prior to plasma delipidation, as opposed to Naficy's separation of blood cells after the delipidation.

- In response to this argument, Naficy's method treats the viruses with ether for 5-30 minutes (Naficy, col. 8, lines 21-31), while Applicant's method treats viruses with ether for one hour. Given the shorter exposure of Naficy's infected blood samples to ether, one would expect that the viral particles of Naficy would not be destroyed, rather reduced in lipid content.
- In response to the separation of blood cells in the instant method versus Naficy's method, Applicant is arguing a limitation that is not in the claims. Regardless, the claims are directed to products. The method by which they are made (Naficy's method or Applicant's) is not expected to result in a structurally and functionally different product, given the similarity of the methods (with the exception of claim 48, which is not rejected.)
- Applicant's assertion that the killed cells could be toxic to the patient is not persuasive to withdrawn the rejection. One of ordinary skill in the art would be able to gauge whether the apheresis method returns blood that is dangerous or acceptable to the patient.

▪ Applicant argues that Naficy's method results in the destruction of the lipid envelope of the HIV virus and destruction of the glycoprotein spikes. Applicant submitted

Exhibit C and the Declaration of Mr. Hassibullah Akeefe under 37 C.F.R. 1.132, showing the treatment of HIV virions with 5% butanol. Applicant points to Example 3, in the instant specification, page 52, line 27 through page 53, line 19. Applicant used 10% diisopropyl ether in a 10:1 ratio, resulting in a final concentration of less than 1%. The result of this experiment was that a significant portion of the viral envelopes is present following delipidation with 1% or 2% solvent.

- In response to Applicant's argument, the Office recognizes that Applicant has demonstrated that with 1% or 2% solvent, HIV envelopes are not destroyed. However, Applicant has not demonstrated that 5% ether destroys HIV envelopes, as asserted by Applicant. Applicant's experiment with 5% butanol is the not the same as Naficy's method using 5% ether.

- Applicant also argues that delipidation under the conditions taught by Naficy does not necessarily result in the claimed partially delipidated viral particles. Applicant points out that there are few details relating to the delipidation method of Naficy. Naficy fails to teach any mixing of solvent and plasma. Applicant argues that the effect of the delipidation process depends on multiple parameters. Applicant asserts that under the conditions of Naficy's direction, delipidation probably leads to destruction of viral envelopes and, as a result, to destruction of viral particles.

  - In response to Applicant's argument, the lack of details with regard to mixing solvent and plasma is not persuasive to withdrawn the rejection. Applicant is arguing limitations that are not in the claims. (Even if such limitations were in the claims, one of ordinary skill in the art would know how to mix the solvent and

plasma. Mixing solvent with plasma does not appear to be the novelty of the instant invention.)

- Applicant also argues that Naficy fails to inherently anticipate Applicant's claimed compositions because Naficy fails to teach the conditions necessary to generate viral particle upon delipidation with 5% solvent, such as mixing conditions, and therefore fails to anticipate the claims inherently.
  - In response to this argument, Applicant is not claiming any particular conditions that render the finished product structurally and functionally different from Naficy's product. While Applicant's experiment with 5% butanol resulted in destructed viral envelopes, Applicant has failed to match Applicant's 5% ether experiment.
- Applicant argues that Naficy teaches the disappearance or elimination of viral infectivity upon delipidation, which shows that the delipidation conditions used in Naficy destroyed viral particles. Applicant argues that Naficy teaches no recovery of infectivity of up to 7 logs of virus after incubation with 5% diethyl ether at room temperature for five minutes. In contrast, Applicant's method results in a 2.5 log reduction in infectivity of immunodeficiency virus upon delipidation, with the remaining virus titer of $10^{4.5}$.
  - In response to Applicant's argument, the claims do not recite the limitations referred to in the argument. While claim 51 is limited to a viral particle that has an infectivity reduced by no more than 2.5 log units, the claim does not recite how the viral particle was made. Applicant's result of infectivity reduced by no more

than 2.5 log units is limited to a particular method of the instant specification. The claims of Naficy and the instant claims are drawn to the same structural components. Lacking any distinguishing structural features (such as method steps that result in the limitation in claim 51), Applicant's composition and Naficy's composition are expected to function in the same manner. In other words, the specific results claimed in claim 51 are not typical of the entire scope of the claims, only a particular method within the specification. The method of the instant specification involves a specific solvent and solvent concentration, minimally. Without these limitations, the claims still read on Naficy's method.

Declaration of Mr. Hassibullah Akeefe under 37 C.F.R. 1.132

6. The declaration has been fully considered. Each of the relevant points of the declaration are addressed below:

- Points 1 and 2 disclose the identify of Mr. Akeefe and familiarity with the instant application and the Naficy patent.
- In Point 3, Mr. Akeefe describes Exhibit C (electron micrographs) and the conditions under which the pictured viruses were produced. In summary, with increasing solvent concentration, the lipid envelope of viral envelopes is destroyed. In particular, the micrographs reflect the destruction of the viral envelope comprising envelope-associated proteins and destruction of partially delipidated immunogenic viral particles upon delipidation with 5% butanol.

- In Point 4, Mr. Akeefe offers his opinion that Naficy teaches the disappearance of viral infectivity upon delipidation. Naficy teaches no recovery of infectivity of up to 7 logs of virus after incubation with 5% diethyl ether at room temperature for five minutes. In contrast, Applicant's method results in a 2.5 log reduction in infectivity of immunodeficiency virus upon delipidation, with the remaining virus titer of $10^{4.5}$. Mr. Akeefe admits that no experiments described in Naficy were performed by Mr. Akeefe, however, the electron micrographs (Exhibit C) demonstrate that delipidation using 5% or more solvent would result in destruction of viral particle integrity.

In response to the declaration of Mr. Akeefe, the Office does not find the declaration persuasive to withdrawn the rejection over Naficy. The problem is that no experiments described in Naficy were performed by Mr. Akeefe. The experiment performed by Applicant was a different experiment than the one described in Naficy. The experiment of Applicant used a different solvent. Without having actually demonstrated destruction of viral envelopes using the same conditions as taught by Naficy, one would not be able to conclude with any certainty that viral envelopes were obliterated. Therefore, the declaration has been considered, but is merely opinion as there is no evidence supporting the assertions regarding Naficy's product.

Conclusion

7. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 4/13/06

Stacy B. Chen
Primary Examiner
April 13, 2006